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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,968	04/20/2001	Michael B. Foster	RENAS/03	1662

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	13

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,968	FOSTER, MICHAEL B.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-3, 5-11 and 13-16 are pending.

Applicants' amendment (Paper No. 11) and Declaration of Dr. Michael Foster (Paper No. 12) filed on February 19, 2003 are acknowledged, and applicants' response has been fully considered. Claims 7 and 13 have been amended, and claims 4 and 18 have been cancelled. Thus, claims 1-3, 5-11 and 13-16 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

2. The previous rejection of claims 7 and 13 under 35 U.S.C. 112 second paragraph, regarding the term "insulin like growth factor levels", is withdrawn in view of applicants' amendment to the claim and applicants' response at page 4 in Paper No. 11.

Claim Rejections - 35 USC § 102

3. The previous rejection of claim 4 under 35 U.S.C. 102(b) as being anticipated by Drake *et al.* (J. Clinical Endocrinology 47, 571-581 (1997)), is withdrawn in view of applicants' cancellation of the claim in Paper No. 11.

4. The previous rejection of claims 4 and 18 under 35 U.S.C. 102(a) as being anticipated by Murray *et al.* (Clinical Endocrinology 52, 537-542 (May 2000)), is withdrawn in view of applicants' cancellation of the claim in Paper No. 11.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2, 3, 10, 11, 13, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 2, 3, 11, 15 and 16 are indefinite because of the use of the term "said maintenance dose is calculated from a daily dose to a monthly dose based on individualized bioavailability data" or "said dose producing said optimal response is calculated from a daily dose to a monthly dose based on individualized bioavailability data". The cited term renders the claim indefinite, it is unclear what is "an individualized bioavailability data", since neither the specification nor the claim define the term, and how the maintenance dose, which is a daily dose as defined in claim 1 or 14, can be calculated from a daily dose to a monthly dose based on the individualized bioavailability data. Claims 3 and 16 are included in this rejection for being dependent on rejected claims and not correcting the deficiency of the claims from which they depend.

In response, applicants indicate the Declaration of Dr. Michael Foster and the specification has shown how the maintenance dose is determined, how the monthly dose is administered, and how the monthly dose is calculated by determining individualized bioavailability data, thus one skilled in the art knows how to calculate a maintenance dose from a daily dose to a monthly dose based on individualized bioavailability data (pages 3-4 of the response; page 6, line 16-page 7, line 9). The response has been fully considered, however, the argument is not found persuasive because the specification has not defined the term "individualized bioavailability data" and how they are determined, and how to convert a daily dose to a monthly dose using the individualized bioavailability data. Furthermore, the

maintenance dose, e.g., cited in claim 1 is defined as a daily dose not a monthly dose, thus it is not clear how to convert a daily maintenance dose to a monthly maintenance dose based on the individualized bioavailability data.

7. Claims 10, 11 and 13 are indefinite because the claim (the clean copy) does not cite the step of "administering said dose producing said optimal response as a maintenance dose". Claims 11 and 13 are included in this rejection for being dependent on rejected claims and not correcting the deficiency of the claims from which they depend.

In response, applicants indicate claim 10 does recite the term (page 4 of the response). The argument is not persuasive because the clean copy of the amended claim (pages 2-3 of the amendment filed September 23, 2002, Paper No. 7), which has been entered, does not recite this term, although the marked copy recites this term.

8. Claim 11 recites the limitation "said dose producing said optimal response" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. See Paragraph 7.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 7-10 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Drake *et al.* (J. Clinical Endocrinology 47, 571-581 (1997)).

Drake *et al.* teaches a method for optimizing growth hormone replacement therapy in hypopituitary adult; the method comprising determining the levels of insulin-like growth factor-1 (IGF-1; claims 7 and 13) or IGF binding protein 3 (IGFBP-3) in response to an initial dose (0.8 or 0.4 IU daily) of hGH (Genotropin, claims 1, step 1), adjusting the dose of hGH until serum level of IGF-1 between the median and the upper end of the age-related reference range is achieved (claim 1 (steps 2 & 3)), establishing the dosage of hGH needed to maintain target IGF-1 levels, and administering the established dose of hGH (Claims 1 (step 4) and 10; page 3914; Fig. 1). The initial dose of 0.8 or 0.4 IU daily (1 IU = 330 μg) corresponds to 5.5 or 2.8 μg/day/kg for female (assuming 48 kg), which is about 4 μg/day/kg (claim 9), or, 3.8 or 1.9 μg/day/kg for male (assuming 70 kg), which is about 2 μg/day/kg (claim 8).

In response, applicants indicate the Declaration of Dr. Michael Foster has shown Drakes does not disclose each and every limitation of the claims, e.g., the reference discloses a uniform titration regimen based on a defined target range of serum IGF-1, however, the claimed invention does not have a defined target, rather an individualized dose (pages 4-5 of the response). The response has been fully considered, however, the argument is not persuasive because although the claim recites using an individualized maintenance dose to replenish hGH, however, the specification indicates these maintenance doses, which produced the desired level of hGH replenishment for the individuals, are typically about 10-14 μg/kg/day for males and about 14-20 μg/kg/day for females, and the levels of IGF-1 serves as mediator of anabolic effects of hGH therapy (page 6, lines 4-15); and all three Examples of hGH therapy (pages 7-12 of the specification) indicate the IGF-1 of each individual is stable about 300 ng/ml on a daily dose of 600 or 800 μg/day in the treatment. Thus, as indicated in the specification, it appears there is a

target range of desired levels of IGF-1 for hGH replacement therapy in the claimed invention. Therefore, the claimed invention is anticipated by Drake *et al.*

10. Claims 1, 5-10, 13 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Murray *et al.* (Clinical Endocrinology 52, 537-542 (May 2000)).

Murray *et al.* teaches using an individualized low-dose titration regimen for a growth hormone replacement therapy in adult with GH deficiency; the method comprising determining the levels of insulin-like growth factor-1 (IGF-1; claims 7 and 13) in response to an initial dose (0.8 IU daily) of hGH (Genotropin, claims 1 & 14 (step 1)), adjusting the dose of hGH by 0.2 or 0.4 IU/day increments until serum level of IGF-1 reaches in the range of the age-related mean for the normal population (claims 1 & 14 (steps 2 & 3); page 538), establishing the dosage of hGH needed to maintain target IGF-1 levels, and administering the established dose of hGH (claims 1 (step 4) and 10; page 539; Table 1). The initial dose of 0.8 IU daily (1 IU = 330 μg) corresponds to 5.5 μg/day/kg for female (assuming 48 kg), which is about 4 μg/day/kg (claim 9), or, 3.8 μg/day/kg for male (assuming 70 kg), which is about 2 μg/day/kg (claim 8). The median value of the maintenance dose for female is 1.6 IU/day (range 0.4-2.4), which corresponds to 11 μg/day/kg (range 2.8-17; page 539; claims 6 and 14 (step 4)). The median value of the maintenance dose for male is 0.8 IU/day (range 0.4-2.0), which corresponds to 3.8 μg/day/kg (range 1.9-9.4), the maintenance dose of 9.4 μg/day/kg is about 10 μg/day/kg (claim 5) absent definition in the specification.

In response, applicants indicate the Declaration of Dr. Michael Foster has shown Murray does not disclose each and every limitation of the claims, e.g., Murray's admission that "the ideal dosing regimen and determinants of maintenance dose have, yet to be elucidated", while the

invention provides the ideal dosing regimen and determinants of the maintenance dose. (page 5 of the response). The response has been fully considered, however, the argument is not persuasive because the statement made by Murray is an opinion as indicated in the Declaration, and Murray has shown GH dose required in an individual is dependent on the serum IGF-1 levels, and an individualized low-dose titration regimen aimed at normalization of the serum IGF-1 is used for GH therapy, which is also indicated in the claimed invention as shown in the section above. Therefore, the claimed invention is anticipated by Murray *et al.*

In the Declaration of Dr. Michael Foster, Paragraphs one and two state he is an inventor and his education and career background; Paragraphs 3 and 4 state the specification provides the information on the maintenance dose, the monthly dose and the calculation of the monthly dose based on the individualized bioavailability data, thus one skilled in the art knows how to calculate a maintenance dose from a daily dose to a monthly dose based on individualized bioavailability data; Paragraphs 5-7 state the difference between the references of Drake and Murray, and the claimed invention; Paragraphs 8 and 9 state the specific difference between Drake and the claimed invention, e.g., Drake discloses a uniform titration regimen based on a defined target range of serum IGF-1, while, the claimed invention does not have a defined target, rather an individualized dose; Paragraphs 10-12 state the specific difference between Murray and the claimed invention, e.g., Murray has used IGF-1 levels to predict maintenance hGH dose, while the claimed invention has accounted the effect of estrogen. Declaration of Dr. Michael Foster has been fully considered, however, it is found not fully persuasive because the specification has not demonstrated how to convert a daily dose to a monthly dose using the individualized bioavailability data as indicated in the paragraph 6; and both Drake and Murray

disclose an individualized low-dose titration regimen for a growth hormone replacement therapy as indicated in paragraphs 9 and 10. Therefore, the claimed invention is anticipated by these references.

Conclusion

11. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

May 14, 2003

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